

Artigo de Revisão/Review Article

Reflections on the medical treatment of endometriosis: an important contribution which could be more widely used

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ABSTRACT

Surgery remains the main treatment for endometriosis. But it does not always obtain the expected results, for reasons which will be analyzed. Sensitivity of lesions to sex hormones, even if not completely perfect, offers a complementary therapeutic possibility, which is not used as much as it should be.

Arguments are developed in favour of the rational use of medical treatment for endometriosis, based on physiological observations and clinical experience.

INTRODUCTION

Treatment of endometriosis is difficult. It is essentially surgical, but medical and hormonal treatment can bring a useful complement to patients. However, the latter forms of treatment are too often criticized and slandered.

Arguments are developed in favour of medical treatment, either on its own or in association with surgery. Those reflexions are personal and do not have any claim to universality. They are written by a Gynecologist with a purely medical and endocrinologic culture, and who has never practised surgery. Endometriosis is an illness with a large variety of presentations and its treatment varies according to the patient's complaints, age, type of lesions, previously received treatment and even local circumstances. But reflections of a general order will always be of interest. At the beginning of this century what are the key elements needed to build therapeutic guidelines?

I. Surgical treatment

Surgery remains the basis for treatment of endometriosis and has evolved significantly during the last 30 years. It brought invaluable benefits to women suffering from this disease. When practiced by specialized surgeons it gives very satisfactory results in about 80% of patients¹. It is clear however, that in its present state, it does not solve all the problems in treatment of endometriosis.

Three points are worth analysing, taking into account the very long length of evolution of this illness, extending sometimes over more than 10 years.

1) Recurrences are frequent even when the surgeon is specialized.

An indirect, though very demonstrative example, is provided by Vercellini et al. who published a comparative study on the effects of intra-uterine system Mirena insertion after surgery for severe dysmenorrhoea caused by endometriotic lesions. During the year

that followed surgery, pain recurred in 45% of women where Mirena had not been inserted². In another publication by the same team, rates of recurrence oscillated between 16 and 33% within the next two years. According to Koga et al., during a 2-year post-operative follow-up, recurrence rate for endometrioma was 30.4% (68/224)³.

More recently, Descamps reported the following figures from a review of the literature (personal communication): painful recurrences 10-75 %; ultrasonographic recurrences 3-19 %; iterative surgery 6-22 %. But the length of the follow up was not provided, because this varied between publications. It is also necessary to take into consideration the **loss of patients during follow-up** which is usually high.

The long evolution of this pathology makes the conduction of randomised studies practically impossible, due to the high costs involved.

2) Postoperative adhesions

These are a natural consequence of surgical tissue trauma and healing, and may result in infertility, pain and bowel obstruction. In studies conducted by the Surgical and Clinical Adhesions Research Group “*approximately one third of patients who underwent open abdominal or pelvic surgery were readmitted an average of two times over the subsequent 10 years for conditions directly or possibly related to adhesions or for further surgery that could be complicated potentially by adhesions.*”. Open and laparoscopic gynecologic surgery were associated with comparable risks for adhesion-related hospital readmissions⁴.

The French laparoscopist Dubuisson, in an interview on the characteristics of endometriosis states that “*every surgical act which is by itself aggressive and traumatic, increases the risks factors of adhesions. Those adhesions are often impressive as they are real weldings which cannot be treated; they have been described as frozen pelvis after surgery on ovarian endometrioma in the young patient ... and he adds: women become often sterile, not because of endometriosis but of surgery (...)* Surgery must be as atraumatic as possible and must adhere to microsurgical principles”.

Therefore, before deciding on an operation the gynecologist should think of the possibility of these complications and discuss them with the patient. This is particularly true in cases of recurrent ovarian surgery⁵. Such repeat surgeries are also not recommended by Chapron et al., who add that “*in case of infertility, management of endometriomas is controversial*”⁶.

These risks are most likely the reason for the consensus statement endorsed by the Chronic pelvic pain/Endometriosis working Group: “*For women in whom endometriosis is the suspected cause of the pain, laparoscopic confirmation of the diagnosis is unnecessary, and a trial of medical therapy, including second-line therapies (...) is justified provided that there are no other indications for surgery such as the presence of a suspicious adnexal mass*”⁷. This does not coincide with ACOG guidelines, which advise, even in the case of adolescents, to perform laparoscopies in women thought to suffer from adhesions or endometriosis⁸.

3) Surgery for deep endometriotic lesions

Surgical results are much better when eradication of lesions is obtained, and in our experience, definitive healing is accomplished in many patients followed for more than 15 years. To remove lesions completely, the surgeon may need to take more risks when faced with deep endometriotic lesions. Complications are more prone to happen in these cases, and some with serious results. The indications for surgery are therefore difficult to agree on. These difficulties are patent in an editorial by Canis and Mage: “*Surgeons! Pity patients who suffer from endometriosis!*” which recalls the dilemma faced by surgeons when confronted intra-operatively with a form of endometriosis that is much more severe than previously thought⁹. The role of high-level teaching of surgical techniques is essential in this context, due to the seriousness of complications that can result from these operations. Some of these issues may be avoided by exhaustive pre-operative exploration involving radiological investigations. Finally, as will be seen later, a multidisciplinary approach, looking at the advantages and disadvantages of first intention surgery, can be of a great help.

For decision-making, an observation by Koga et al. should, if confirmed, be kept in mind: “previous medical treatment of endometriosis or large cyst size was a significant factor that was associated with higher recurrence of the disease”. But the study was retrospective and the administration of drugs was not randomised, nor did it have placebo controls³.

II. Medical treatment

Medical treatment is currently underused and subject to much criticism, especially due to the brevity of its action - it is active only as long as it is taken, and recurrences happen as soon as it is interrupted. But this criticism can be applied to almost all treatments of chronic diseases and clearly endometriosis pertains to this group. The short-term action of medical treatment is not a valuable argument to disregard it. One has only to consider that it must be prolonged during years and not months to increase its efficiency.

Non steroidal anti-inflammatory drugs of various kinds, analgesics, LH-RH analogs, progestins alone or combined with estrogens, and more recently developed modern drugs such as antiprogestins and antiestrogens, which are still under investigation, such is the range of medications that can be used to treat endometriosis. It is not useful or possible in this article to describe in detail all of these different forms of treatment. We shall focus in the requirements necessary for the prescription of a small number of them, as their specific characteristics are sometimes insufficiently taken into account.

1) *Gonadotrophyn releasing hormone (GnRH) agonists*

These are powerful tools to suppress ovarian function but the flare up they provoke is not always taken into account, and thus the choice of the date of first injection is often inadequate. An example of this is found in the article by Vercellini et al.¹⁰ who reported that aspiration and washing of endometriotic cysts, whether or not combined with post-operative administration of GnRH agonist, was ineffective. The authors add that “*this finding could be explained by the initial gonadal stimulation (by GnRH agonist), which lasted one to two weeks, with a consequent rise in blood 17*

â-estradiol (...) and subsequent withdrawal bleeding (...). This pseudomenstruation may have partly filled the cystic cavities again before the first follow-up US scan”. But what is retained in the mind of the readers is the inefficiency of GnRH agonist treatment of endometriomas, which was in fact incorrectly used, as generously recognized by the renowned team.

Surgeons are usually not favourably inclined to the use of hormonal treatment after an operation. Yap et al. conclude in their systematic review that “*there were no trials identified in the search that compared hormonal suppression of endometriosis before and after surgery with surgery alone*”¹¹. Yet all surgeons are aware of the risks and frequency of recurrences. Winkel and Bray¹² report on the outcome of 61 endometrioma cases after follow up (Table I).

Table I. Recurrence of symptoms of 61 cases of endometrioma submitted to two different types of treatment.

	N	6 months	18 months
Surgery alone	13	11	0
Surgery + GnRH agonist	48	0	1

A second problem related to the use of GnRH agonists is bone mass loss and other side effects due to the hypoestrogenism. Add-back therapy can reduce these problems and allow therapy to be administered for more than 6 months. But methods of add-back therapy are numerous and selection of the best is difficult. Hence this very efficient option is less used than it should, or regimens with less efficiency and more side effects are selected. One point that cannot be denied is that it is expensive.

2) *Progestins*

Vercellini et al. wrote in a remarkable review on the use of these drugs: “*The paucity of scientific interest in progestins in recent years is inexplicable*”¹³. All progestins can induce anovulation and hypoestrogenism if given for more than 18 days a month, or if taken continuously, which is a more efficient regimen. But “*amenorrhea is beneficial and side effects are tolerable*”¹³.

The recurrence rate after their withdrawal is reported to be around 50% after 6 months. For this reason they should be taken for longer than half a year, and if signs of severe hypoestrogenism appear, estrogens can be administered in a weak dosage.

It is well known by French gynecologists that when the patient's pain is not alleviated by conservative recurrent surgery, and the patient does not accept the idea of hysterectomy, progestins can be used as a last resource. In such cases, progestins belonging to the pregnane or norpregnane family can be used (cyproterone acetate and dienogest have also proved their efficiency).

One can understand that surgeons favour an operative approach and do not appreciate the protracted prescription of progestins, but maybe this idea needs to be questioned. A striking example is given in a study by Jacques Donnez, a renowned pioneer in the treatment of endometriomas. In 814 patients undergoing laparoscopy for ovarian endometriotic cysts, the cyst was incised, the chocolate-coloured fluid aspirated, and the cyst wall underwent biopsy. Patients then received 4 monthly injections of goserelin acetate. Twelve weeks after the first laparoscopy, the patient was re-intervened and the cyst wall vaporized with CO2 laser. The cumulative pregnancy rate was 51% at one year and the recurrence rate was 8% for the women followed 2-13 years¹⁴. If one considers that only 150 women desired to become pregnant (*from fig. 1 of the article it appears that 42 pregnancies were obtained during the first month - 30% of the total number of pregnancies*), why not administer progestins in a small number of patients, to avoid the second laparoscopy and observe their effects?

Progestins are of course not a panacea. Some women do not tolerate their side effects: increased weight, loss of libido and diurnal somnolence, making it necessary to use other medications.

3) Combined oral contraceptives

These drugs are only indicated in minimal and mild endometriosis, and mainly in cases of severe dysmenorrhea. As endometriosis is a disease characterized by cyclic bleeding, extending the duration of contraceptive pills to 6-12 weeks or longer decreases the

frequency of menstrual related pain¹⁵ and produces satisfactory results in about 80% of patients¹⁶.

Sulak et al. observed that results were better when the patient herself chooses the duration of extension; and that analgesics can be added when needed. Spotting, bloating, and headaches are infrequent side effects, but may be the cause of interruption¹⁷. In a second publication by the same author, 172 patients out of 267 chose extended regimens (endometriosis represented only 12% of the patients). Forty-six per cent of these women followed this regimen for 5 years or more. The mean duration of continuous intake was 12 weeks (and in one case 112 weeks) and the mean hormone free interval was $6 \pm 2d$ ¹⁸.

4) Levonorgestrel intrauterine system

Levonorgestrel intrauterine system (LNG-IUS) is a very particular form of extended progestin treatment which is often efficacious in patients who are very disabled by their pelvic pain^{19,20}. This effect is still partially unexplained, since the LNG-IUS does not inhibit ovulation and acts mainly on the endometrium. Pain improvement is not constant and the LNG-IUS sometimes has undesirable effects, although they usually fade with time. However, it is surprising that gynaecologists do not take advantage of the frequent hormonal sensitivity of endometriotic lesions more often, as for instance in the case of rebel dysmenorrhoea.

5) Injectable progestins

The efficacy and safety of subcutaneous depot medroxyprogesterone acetate (DMPA) seems to be established. It has been compared with leuprolide acetate in the treatment of endometriosis-associated pain, given every 3 months for a total duration of 6 months, with a 12 month post-treatment follow-up. Efficacy of DMPA was equivalent to that of leuprolide, but with less impact on bone mass and fewer hypoestrogenic side effects, but more bleeding²¹.

6) The risks of progestins

It must not be forgotten that prolonged administration of progestins to premenopausal women appears to increase the risk of breast cancer by about 40% after 4 years²³.

7) *Successive or synchronous associations*

GnRH agonists, progestins, danazol in weak doses (20-50 mg/day - which can be inserted in the vagina in cases of recto-vaginal endometriosis), and also natural estrogens, can be given in association during variable periods or administered successively. Treatment can be tailored to minimise undesirable effects. It is likely that anti-oestrogens (in the form of antiaromatases) as well as antiprogestones will cause a quick ovarian quiescence with lesion rest, creating a state of amenorrhoea and abolishing a sometimes extremely severe dysmenorrhoea, which is often the only desire of patients.

8) *Colchicine*

Colchicine is an anti-inflammatory drug which inhibits the synthesis of TNF alpha by macrophages, and also has anti-angiogenic effects²³. As it suppresses serosal inflammation, it is very effective in preventing familial Mediterranean fever attacks, when taken continuously for years. We have used it (0.5 or 1 mg/day alone or with opium powder) in many patients suffering from painful endometriosis, noting a prolonged but sometimes incomplete efficacy. In two cases, an unexpectedly pregnancy occurred shortly after the start of treatment. In some patients with previous recurrent operations it has proved useful as a means to avoid further surgery. It may therefore be a therapeutic option in such situations.

III. Consequences of recent progresses in this field

Both surgical and medical therapies of endometriosis can benefit from recent progresses in this field. Two of these progresses have already been universally accepted, and relate to the use of non-invasive methods for investigation of the disease and the option of assisted reproduction technology (ART) to treat infertility. The third is only now beginning to be perceived, and relates to psychological aspects of the disease.

1) *Progresses of radiology*

Radiologists have for long described the characteristic signs of the endometriomas. This relatively easy diagnosis has had a negative impact on the life of some women. As soon as the gynaecologist announces the existence of an

endometriotic ovarian cyst, many women ask to be disencumbered of it. But in fact, many recent publications have shown that these cysts have little influence on fertility, particularly in cases where ART treatment is chosen^{24,25,26}. It is of course always necessary to be aware of the possibility of malignant lesions or borderline tumours, but their frequency has probably been exaggerated in the past²⁷. Since the importance of deep endometriosis was recognized, radiologists have improved their recognition of this entity by ultrasound, as well as by MRI.

Of course, not all radiologists will be capable of interpreting MRI images correctly, but more and more are gaining experience in this area. Gynecologists must also strive to better understand methods for visualisation of endometriosis lesions, and to collaborate with radiologists to improve knowledge in this area.

The same holds true for ultrasound, and every effort should be made to undertake these methods of investigation before a laparoscopy is decided²⁸.

2) *Assisted Reproduction Techniques*

Results of ART in endometriosis are now generally recognised as good enough to balance against the results of surgery. A renowned French expert in ART and endometriosis surgery, JL Pouly, reported the following pregnancy cumulative rates after four in-vitro fertilisations: endometriosis 44%, pure tubal infertility 40.3%. As the use of in-vitro fertilisation in France has been rapidly increasing, ART for endometriosis alone represented 2.7% of cases in 1992 and 6.1% in 2002²⁹.

Hence, before advising any woman with endometriosis-related infertility to undergo surgery, the gynecologist should point out that the risk of inducing new adhesions needs to be considered, and that ART can be a good alternative, especially in cases of endometriomas. Seeking complementary information at an ART centre can also help women decide. Nevertheless, surgery continues to provide excellent results - more than 50% of patients becoming pregnant during the first year - and remains an extremely valid option for treatment of endometriosis-related infertility.

3) *The psychological aspect of endometriosis*

For many years, gynecologists have been surprised by tales of psychological traumas and abuse, often of a

sexual nature, especially during adolescence, from endometriosis patients. But only a small summary of this important area of knowledge will be provided here. With JP Allart, we turned our attention to the history of emotional shocks in endometriosis patients, but avoiding any particular emphasis on this aspect. We observed in 1999 that 95 out of 200 patients, and in 2005, 153 out of 300 patients, had suffered from sexual abuse, unearned physical punishments, or from abandonment. Moreover, several patients reported that psychological disturbances had seriously affected their choice of partner. Insecurity and inadequate sexual response was also referred, leading to serious problems with the partner, and perpetuating emotional instability. Importantly, in about 50% of endometriosis patients no such factors can be found, and the existence of a genetic factor is the most probable explanation³⁰.

Several reports of the importance of psychological aspects in endometriosis can be found in the literature. John Rock, in 1993, writing about pelvic pain related to endometriosis stated: *“organic and functional causes are multiple, and contributing factors are complex. These include sexual dysfunction and conflict, affective disorders, a history of sexual abuse, and other detrimental developmental experiences”*³¹.

More recently, another North American team obtained more objective proof of the emotional instability of endometriotic women³². They studied a young patient's reflexes linked to stress - digital temperature, skin sweat response, electroencephalography, skeletal muscle activity - and concluded: *“endometriosis symptoms were associated with physiological measures indicating prolonged stress reactions for the symptomatic woman and her parents. Facts of family history and relationships for three generations set the stage for stress reactions. Striking differences are evident in the physiology, family history, and contact with family of the nonsymptomatic woman”*.

Such a history of emotional trauma may provoke a lower threshold for pain, but it can also be hypothesised that it favours grafting of endometrial cells in the peritoneal cavity. The link between these disturbances and endometriosis would imply an impairment of immunological defences (possible the role of neuropeptide Y) favouring survival of the graft. Another

mechanism could be the exaggeration of tubal motility, due to a neurovegetative imbalance, and consequent increased reflux into the peritoneum.

Proof of a direct relation between prolonged emotional shock and endometriosis is not absolutely essential for the clinician, but it is important that he is aware that a disturbance of the psycho-neuro-endocrino-immunological axis can exist in this apparently very organic disease. As there maybe a link between patient complaints an anxiety preceding the appearance of the endometriosis, it is also important to adjust medication with this information in mind.

Today this question seems to have advanced, as shown by the remark of Rodolphe Maheux, who died while chairing the World Endometriosis Society: *“the surgeon (...) who only thinks, for instance, to eradicate the lesions of endometriosis, and who does not consider all living of the patient will often have few successes and many recurrences. The key to taking good charge is therefore to act on both aspects: psychological and physical”*. But difficulties persist, as patients, persuaded of the organic nature of their disease do not always accept well the idea of psychotherapy. It is therefore necessary for the gynaecologist to explain to patients that their past traumas may be contributing to current health problems and further evaluation by a specialist in this area would be beneficial⁸. Psychological support, psychotherapy, acupuncture etc. may be of a great help and constitute and important aid to medical treatment.

IV. The FOATI classification

We would not like to end this reflection without mentioning the French classification of endometriosis³³. Even if universally used, the ASRM classification does not seem to meet its objectives, as it has limited prognostic value and does not help to decide treatment. On the other hand, the importance of radiology is not forgotten in the FOATI classification (Foci, Ovary, Adhesions, Tubes, Inflammation), describing all existing lesions and not only lesions visible by laparoscopy. It provides immediate information on the dominant lesion and helps decide therapeutic indications. For instance: peritoneal implants – should be medically treated, because hormones have the best risk/benefits ratio.

CONCLUSION

It appears to be increasingly clear that endometriosis will be best treated in a multidisciplinary centre: a hospital specially dedicated to its treatment, or a clinic with physicians working towards the same goal.

Probably, when there is no doubt about the nature of the disease and no risk of malignancy, in many cases surgery should be chosen only after failure of medical treatment. And complementary hormonal treatment pre and/or post should be considered more often than before.

Medical treatment has several advantages over surgery but must be administered for much longer time periods than currently employed by the majority of clinicians. The main advantage of medical treatment is that its effects are reversible and can be followed by surgery in patients who do not respond adequately to it.

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